Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology

# CBER Surveillance Program

## Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring

## Protocol Addendum

December 29, 2021

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# 1. Overview

This document is submitted as an addendum to the Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring Protocol.[1] The purpose of this addendum is to clarify the data sources used for the analyses and to specify the analytic approach to estimate the background rates of the adverse event of special interest (AESI), thrombosis with thrombocytopenia syndrome (TTS), including unusual site TTS and common site TTS. We note that the TTS definition differs slightly from the Brighton Collaboration interim case definition for TTS.[2]

# 2. Data Sources

The analyses detailed in Section 3 of this addendum, along with all analyses identified in the original protocol, will be conducted in the administrative claims databases referenced in Section 2.1 of this addendum.

## 2.1 Administrative Claims Data Sources

Available data sources include adjudicated claims in IBM® MarketScan® Commercial Database, Blue Health Intelligence® (BHI®), HealthCore, CVS Health's Aetna commercial and Medicare Advantage databases, pre-adjudicated[3] Optum commercial claims, as well as adjudicated claims from Centers for Medicare & Medicaid Services (CMS) Medicare Fee-for-Service (FFS) data.

The MarketScan Commercial Database contains more than 25 million annual enrollees for active employees, early retirees, Consolidated Omnibus Budget Reconciliation Act (COBRA) continuees, and dependents insured by employer-sponsored plans. The MarketScan Research Databases capture individual-level clinical utilization, expenditures and enrollment across inpatient, outpatient, prescription drug, and carve-out services from a selection of large employers, health plans, and government and public organizations.

BHI data provide HIPAA compliant, deidentified enrollment, demographic, and claims information from the majority of Blue Cross and Blue Shield commercial health insurance plans in the United States for the last ten years. While the BHI database includes more than 200 million unique lives, detailed data for this study was limited to a cohort of all enrollees who received a biologic product, were pregnant, or were born after October 1, 2015. Pregnant women are identified via codes for prenatal care, gestational age, or pregnancy outcomes. Currently, the BHI cohort population for this study contains over 34 million individuals in total and about 17 million enrollees annually, on average. Approximately 350,000 pregnancy outcomes are observed annually. BHI data are updated monthly and are over 80% complete within 4 months of the service date.

Commercial insurance claims data in the HealthCore Integrated Research Environment (HIRE) combines medical and pharmacy claims, and laboratory results, drawn from nearly 76 million unique individuals with medical coverage, with approximately 59 million also

[1] https://www.bestinitiative.org/wp-content/uploads/2021/02/C19-Vaccine-Safety-AESI-Background-Rate-Protocol-FINAL-2020.pdf
[2] Brighton Collaboration. *Interim Case Definition of Thrombosis with Thrombocytopenia Syndrome (TTS).* Brighton Collaboration; May 18, 2021 2021. https://brightoncollaboration.us/thrombosis-with-thrombocytopenia-syndrome-interim-case-definition/
[3] After a claim for medical service(s) or prescription drug(s) is submitted, the insurer determines their financial responsibility for the payment to the provider or the pharmacy. This process is referred to as claims adjudication. The insurer can decide to pay the claim in full, deny the claim, or to reduce the amount paid to the provider or the pharmacy. Due to the time requirement for the adjudication process, a database of adjudicated claims will have a longer lag time than the pre-adjudicated claims.

having pharmacy coverage dating back to 2006. The data environment contains physician office, outpatient, and ER visits, hospital stays, outpatient surgeries, ambulance transportation, skilled nursing facility episodes, as well as durable medical equipment. The data currently contain over 23 million members in 2020 with a data lag of 3 months for complete data and 1–3 months for pharmacy dispensings and early settled outpatient claims.

CVS Health Clinical Trial Services (CVS CTS) transforms enrollment, demographic, and medical and drug claims data for individuals enrolled from January 2018 forward in Aetna commercial and Medicare Advantage health plans into a patient-centered, comprehensive Common Data Model (CDM). The CDM contains over 37 million individuals in total and on average about 22 million individuals annually. CVS CTS updates monthly with a data lag of approximately 1 week for drug claims, 6 weeks for outpatient, and 12 weeks for inpatient claims for over 80% claims.

The Optum data includes enrollment, prescription drug and pre-adjudicated hospital and physician health insurance claims. The pre-adjudicated claims database includes claims for privately insured and Medicare Advantage enrollees. Hospital and physician claims undergo initial processing on a daily basis from a large number of providers across the U.S. who accept patients with health insurance. Optum has established an ongoing weekly update schedule to incorporate newly processed claims into the pre-adjudicated claims database. This data source was utilized to reduce the delay between the occurrence of healthcare services and their presence in the database. The pre-adjudicated claims have an approximately two-month delay for 90% completeness for inpatient claims and over 70% completeness at one-month for outpatient claims.

CMS Medicare FFS data contain enrollment, demographic, and claims information for all individuals enrolled in Parts A/B (since 1991), Part C (since 2012), and Part D (since 2006). Medicare data currently contain about 34 million current beneficiaries annually, on average. Medicare claims data undergo three stages of processing: enumeration, adjudication, and final payment. Medicare Shared Systems Data (SSD), which consists of claims sourced after enumeration, will be used in this study. SSD is updated daily and is over 80% complete within 30–70 days depending on setting and outcome.

# 3. Methods

## 3.1 Study period

This analysis will be conducted in the same study period referenced in Section 6 of the original protocol, starting on January 1, 2017 for MarketScan, BHI, HealthCore, and CMS data, and on January 1, 2019 for CVS and Optum data, and ending on December 11, 2020 for all data sources. The observation period will start one year prior to the beginning of the study period to allow a 365-day clean period as specified in Section 3.2 of this addendum.

## 3.2 Outcomes

Table A1 summarizes the added TTS AESIs, age groups of interest, care setting, and clean windows that will be used in this analysis. These outcomes are added to the complete list of AESIs in Table 2 of the original protocol.

**Table A1**. List of Thrombosis with Thrombocytopenia Syndrome (TTS) Adverse Events of Special Interest (AESIs)

| Safety AESI | Age Group of Interest | Setting | Clean Window** |
|---|---|---|---|
| **Unusual site thrombosis with thrombocytopenia (Unusual site TTS)** | All | Unusual site thrombosis (including intracranial or intraabdominal venous thromboses, such as in portal, renal, and other veins): IP, OP-ED; thrombocytopenia: IP, OP/PB | 365 days* |
| **Common site thromboses[£] with thrombocytopenia (Common Site TTS)** | All | Acute myocardial infarction, hemorrhagic stroke, and non-hemorrhagic stroke: IP; deep vein thrombosis, pulmonary embolism, and thrombocytopenia: IP, OP/PB | 365 days* |
| **Acute myocardial infarction with thrombocytopenia** | All | Acute myocardial infarction: IP; thrombocytopenia: IP, OP/PB | 365 days* |
| **Hemorrhagic stroke with thrombocytopenia** | All | Hemorrhagic stroke: IP; thrombocytopenia: IP, OP/PB | 365 days* |
| **Non-hemorrhagic stroke with thrombocytopenia** | All | Non-hemorrhagic stroke: IP; thrombocytopenia: IP, OP/PB | 365 days* |
| **Deep vein thrombosis with thrombocytopenia** | All | Deep vein thrombosis and thrombocytopenia: IP, OP/PB | 365 days* |
| **Pulmonary embolism with thrombocytopenia** | All | Pulmonary embolism and thrombocytopenia: IP, OP/PB | 365 days* |

Abbreviations: ED, emergency department; AESI, adverse event of special interest; IP, inpatient; N/A, not applicable.
Setting Definitions: IP refers to inpatient facility claims. OP-ED refers to a subset of outpatient facility claims occurring in the emergency department. OP/PB refers to all outpatient facility,
claims, and professional/provider claims except those professional/provider claims with a laboratory place of service.
* References for these windows could not be found in the literature and are instead based on input from clinicians.
** Clean window is defined as the time period prior to cohort entry, during which an individual had continuous enrollment with no AESI observed.
[£] Common site thromboses include acute myocardial infarction, deep vein thrombosis, hemorrhagic stroke, non-hemorrhagic stroke, and pulmonary embolism

### 3.2.1 Identification of TTS outcomes as composite episodes

TTS outcomes are composite health events requiring co-occurrence of two conditions within a time period. A composite episode of TTS is defined as a thrombotic event and a thrombocytopenia (TP) event within 14 days of each other (the subsequent event date minus the previous event date +1 is less or equal to 14 days), with a total length of ≤14 calendar days including the start date of the episode. The TTS composite event date is defined as the start

date of the composite episode (the earliest date when either thrombosis or TP event occurs in an episode). The composite TTS episode is an operational concept referring to a segment of time (days) when thrombosis and TP diagnoses co-occur within 14 days of one another and is not equivalent to a clinical episode. Further details on clinical codes that identify thrombotic and thrombocytopenia events can be found in the supplemental file[4] which accompanies the original protocol.

The following summarizes the construction of the composite outcome for TTS:

1. During the observational period, thrombosis and TP events, as defined by diagnosis and relevant settings as specified in Table A1, are identified.
2. Starting from the first condition A event (thrombosis or TP), check for a condition B event (thrombosis if condition A was a TP event, or TP if condition A was a thrombotic event) within 14 days of condition A. The 14 days include the date of condition A and 13 subsequent days. If no condition B is found within 14 days, move on to the next event (thrombosis or TP) to search for the other component of the composite outcome.
    a. Repeat this until a composite outcome (thrombosis and TP) is found consisting of a condition A event and a condition B event within 14 days.
    b. Set the composite episode end date as the date of the last condition A or B events (if there are condition A/B events on multiple days after the episode start date), but no later than 13 days after the episode start date.
    c. Set the composite outcome date as the date of the first condition A or B in the episode.
3. Continue the search for subsequent composite episodes after the episode end date of the preceding episode.
4. Place all TTS composite episodes on the timeline during the observational period.

## 3.3 Cohort entry, follow-up, and incident case for TTS composite outcomes

Identification of the study population will follow the specifications in Section 7 of the original protocol, with composite episodes defined in Section 3.2.1 of this addendum as the outcomes of interest. We use the start date of the TTS composite outcome episode for eligibility evaluation, clean window requirement evaluation, determination of cohort entry/re-entry dates, censoring, and the identification of incident events as specified in the original protocol. Figure A1 displays a graphical representation of how to define an incident composite outcome and the third composite outcome episode qualifies the definition as an example.

## 3.4 Analysis in Claims Data Sources

Analyses will follow the specifications referenced in Section 8 (and summarized in Table 4) of the original protocol.

[4] https://www.bestinitiative.org/wp-content/uploads/2021/02/C-19-Vaccine-Safety-AESI-Background-Rate-Supplemental-2021.xlsx

**Figure A1.** TTS Episode Definition